Exhibit H

Final Clinical Study Report

1. TITLE PAGE

Protocol No.: 381.107

Mixed Salts Amphetamine

A SINGLE-DOSE, BIOEQUIVALENCE STUDY COMPARING 1 X 40 MG CAPSULE OF SLI381 TO 4 X 10 MG CAPSULES OF SLI381 IN PEDIATRIC SUBJECTS

July 30, 2002

Investigator	Site # or Affiliation	Location
Samuel W. Boellner, MD	Clinical Study Centers, LLC	Little Rock, AR

Study Start Date: February 16, 2001
Study Stop Date: March 28, 2001

Sponsor:
Shire Pharmaceutical Development, Inc.
1901 Research Boulevard, Suite 500
Rockville, MD 20850

Contact Person: Yuxin Zhang, PhD

This study was conducted in compliance with internal review board and informed consent regulations

2. SYNOPSIS

Name of Study Drug:	IND #:	Protocol No.	Phase:	Country:
Mixed Salts Amphetamine	58,037	381.107	I	USA

Title:
A single-dose, bioequivalence study comparing 1x40 mg capsule of SLI381 to 4x10 mg capsules of SLI381 in pediatric subjects

Principal Investigator/Affiliation:	No. of Study Centers:	Study Period:
Samuel W. Boellner, MD Clinical Study Centers, LLC Little Rock, AR	1	First enrollment date: February 16, 2001 Last completion date: March 28, 2001

Objective:
To determine dose-equivalence of 1x40 mg of SLI381 capsules to 4x10 mg of SLI381 capsules following a single dose administration

Methodology:

This trial was an open-label, randomized, single-dose, two-treatment and two-period crossover study investigating the bioequivalence of an orally administered 1x40 mg SLI381 dose to a 4x10 mg SLI381 dose in pediatric subjects. The study was conducted under medical supervision.

Potential subjects were screened during the two weeks before study initiation (Days –14 to –2). Twenty subjects who fulfilled the inclusion criteria each received a single dose of 1x40 mg SLI381 capsule or a single dose of 4x10 mg SLI381capsules administered orally, with water, in the first dosing period. The alternate dose was administered in the second period. The two dosing days were separated by a 7-day washout. All subjects observed an overnight fast before each of the two test days and standard meals starting 4-hours post dose on test days.

On each of the two test days, blood was collected at pre-dose (hour zero) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, and 48 hours post-dose. Quantitation of plasma d- and l-amphetamine concentrations was performed using a validated LC/MS/MS method. A physical examination, height, weight, blood pressure and pulse, and laboratory tests including hematology, chemistry, and urinalysis, in addition to a urine pregnancy test (for females who had experienced menarche) were conducted at screening and at termination. Blood pressure and pulse were monitored throughout the dosing days. Subjects were questioned concerning their well being prior to dosing at each period and prior to leaving the site on dosing days. Spontaneous adverse events were collected throughout the study.

Author: Sally A. Breisch, MS Amarex Clinical Research	Signature:	Date: 8/6/02
Statistician(s): Safety: Rongde Gui, PhD Amarex Clinical Research	Signature:	Date: 8/6/02
Efficacy: Yuxin Zhang, PhD Shire Pharmaceutical Development Inc.	Signature:	Date: 8/7/02
Approved by: Neil Frazer, MD Vice President of Clinical Research Sponsor's Medical Officer	Signature:	Date: 8/13/02

Name of Study Drug:	IND #:	Protocol No.	Phase:	Country:
Mixed Salts Amphetamine	58,037	381.107	I	USA

Number of Subjects (planned and analyzed):
The protocol called for 20 subjects to ensure a statistical power of more than 80% to conclude bioequivalence between the two dosing regimens. Twenty (20) subjects participated in the study and all completed the study. Data collected from all of the study participants were evaluated for bioavailability and safety.

Diagnosis and Main Criteria for Inclusion:
Pediatric subjects, 6 to 12 years of age, diagnosed as ADHD with prior exposure to stimulants (Adderall®, methylphenidate, dextroamphetamine) at similar dose levels as were given in this study, no clinically significant tolerability difficulties to prior stimulants, and between the 5th and 95th percentile on the National Center for Health Statistics growth chart for age, height, and weight.

Test Product, Dose, Mode of Administration, and Batch Number:
Test drugs were SLI381 capsules provided by the sponsor, each capsule containing 40 mg (lot # 0F2722A) of mixed salts of single entity amphetamines for oral administration.

Duration of Treatment:
This was single-dose, two-period crossover study with a 7-day washout interval between each dose administration. Dosing time was approximately 8:00 am in the morning of each dosing day.

Reference Therapy, Dose and Mode of Administration, Batch Number:
For the purpose of bioequivalence analysis, the 10 mg capsules (lot # 0B2774A) of mixed salts of single entity amphetamines for oral administration were considered as the reference. No other reference drug or placebo was used in the study.

Criteria for Evaluation:
Efficacy (Pharmacokinetics):
Extent (AUC) and rate (C_{max}) of drug absorption and time-to-peak concentration (T_{max}) were evaluated for differences between the two doses using analysis of variance (ANOVA). Analysis of bioequivalence was carried out using the ANOVA model on log-transformed data for AUC and C_{max}, and the 90% confidence interval (CI) was constructed for the ratio of the test-to-reference means from the two 1-sided t-tests approach. The currently used average bioequivalence criteria of 0.80-1.25 limits for log-transformed data were applied to draw conclusions.

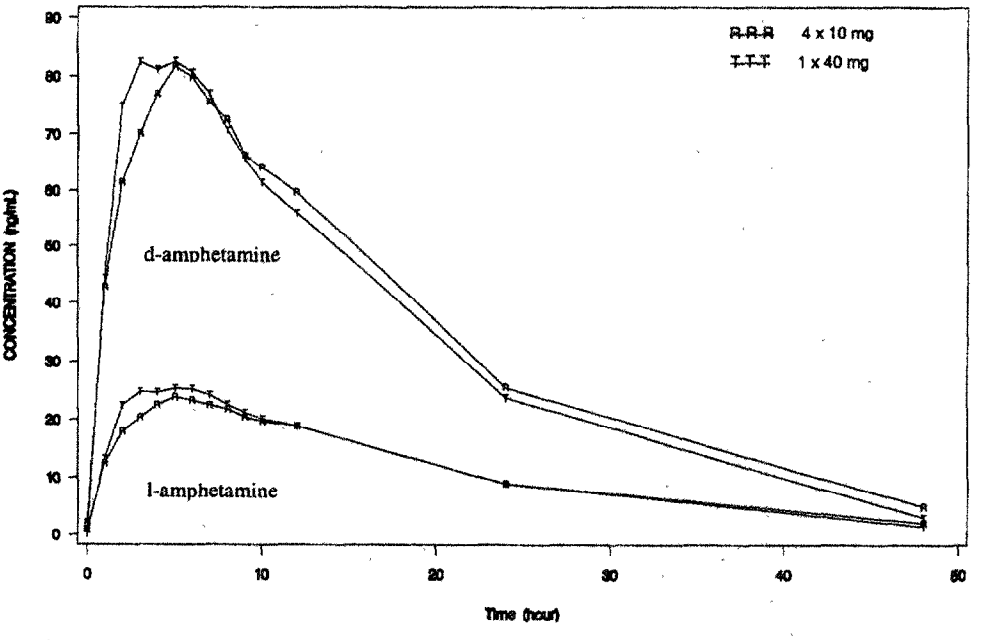
Safety:
All safety parameters collected were assessed descriptively. These parameters included adverse events (AE), clinical laboratory tests (chemistry, hematology, and urinalysis), medical history, physical examinations, 12-lead electrocardiogram (ECG), and vital signs. Vital signs were assessed descriptively and comparatively.

Statistical Methods:
Efficacy (Pharmacokinetics):
Extent (AUC) and rate (C_{max}) of drug absorption and time-to-peak concentration (T_{max}) were evaluated for differences between the two doses using analysis of variance (ANOVA) with a general linear model. Analysis of bioequivalence was carried out using the ANOVA model on log-transformed data for AUC and C_{max}, and the 90% confidence interval (CI) was constructed for the ratio of the test-to-reference means from the two 1-sided t-tests approach. The currently used average bioequivalence criteria of 0.80-1.25 limits for log-transformed data were applied to draw conclusions.

Safety:
Observed adverse events and vital signs were analyzed descriptively. Vital signs were also analyzed comparatively using the paired t-test.

Name of Study Drug:	IND #:	Protocol No.	Phase:	Country:
Mixed Salts Amphetamine	58,037	381.107	I	USA

SUMMARY RESULTS
EFFICACY:



D-Amphetamine

	Parameters (means)			
	AUC (0-inf) (ng.hr/mL)	AUC (0-t) (ng.hr/mL)	Cmax (ng/mL)	Tmax (hr)
1 x 40 mg SLI381 (test)	1573.95	1608.98	98.61	5.35
4 x 10 mg SLI381 (reference)	1688.25	1662.87	92.94	5.64
		Bioequivalence		
Ratio of test-to-reference	1.00	0.97	1.06	
90% CI	0.96 – 1.03*	0.93 – 1.02*	0.96 – 1.16*	

L-Amphetamine

	Parameters (means)			
	AUC (0-inf) (ng.hr/mL)	AUC (0-t) (ng.hr/mL)	Cmax (ng/mL)	Tmax (hr)
1 x 40 mg SLI381 (test)	538.91^	539.33	30.27^	5.45
4 x 10 mg SLI381 (reference)	512.01	529.31	27.16	5.80
		Bioequivalence		
Ratio of test-to-reference	1.06	1.03	1.11	
90% CI	1.02 – 1.10*	0.96 – 1.10*	1.03 – 1.21*	

^ $p<0.05$ compared to 4 x 10 mg SLI381
* Denotes 90% confidence interval fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on logarithmic scale

Name of Study Drug:	IND #:	Protocol No.	Phase:	Country:
Mixed Salts Amphetamine	58,037	381.107	I	USA

SUMMARY RESULTS (continued)

SAFETY:

All 20 subjects reported one or more adverse events during the study. The majority of treatment-emergent adverse events (145/162, 89.5%) were judged as related or possibly related to study medication and mild or moderate in severity (154/162, 95.1%). The 1x40 mg condition had 50.6% (82/162) and the 4x10 mg condition showed 49.4% (80/162) of the total adverse events. Under both dosing conditions, all 20 subjects reported one or more adverse events. Because of the investigator's use of specific criteria for reporting hypertension (systolic ≥ 130 mmHg and diastolic ≥ 85 mmHg and 20% increase from baseline) and tachycardia (≥ 120 bpm and 20% increase from baseline) as adverse events, hypertension and tachycardia were seen as the most common adverse events in the study. The incidence of subjects reporting was 80% for hypertension and 70% for tachycardia. The other commonly reported adverse events included insomnia, dizziness, nausea, anorexia, and headache. All of these adverse events were not unexpected.

Compared to the time of pre dose, significant ($p<0.01$) increases in mean systolic blood pressure were observed for the time period of 2-, 4- and 12-hours post treatment both in the 1x40 mg group and 4x10 mg group. For diastolic blood pressure, significant increases from pre-dose level were noted for the 4x10 mg group at 4- hours post dose. No significant changes were noted in pulse for either of the dosing conditions. No significant abnormal physicals or lab results were reported at study close out.

CONCLUSIONS:

Shire Pharmaceutical Development Inc. has developed a two-component extended-release formulation (SLI381) of Adderall® designed to produce pulsed-release of amphetamine salts yielding a therapeutic effect that lasts throughout the day with one morning dose, for treatment of attention deficit hyperactivity disorder (ADHD).

The objective of this study was to evaluate the bioavailability and bioequivalence of a single 1x40 mg SLI381 oral dose in comparison to a single 4x10 mg SLI381 oral dose in pediatric subjects.

This study demonstrated that a single 1x40 mg dose of SLI381 capsules was bioequivalent as measured by all relevant PK parameters to a single 4x10 mg dose of SLI381 capsules in pediatric subjects for both d- and l-amphetamine. For l-amphetamine, statistically significant differences were noted between the two doses for $AUC_{0\text{-}inf}$ and C_{max} with the 1x40 mg dose being higher, but not for $AUC_{0\text{-}t}$.

Additionally, the two SLI381 doses were similarly tolerated. All 20 subjects reported one or more adverse events during the study. The incidence of subjects reporting adverse events was the same for both dosing conditions. The majority of adverse events were mild or moderate in severity and judged as treatment related or possibly related. The most frequently reported adverse events were not unexpected (i.e., hypertension, tachycardia, insomnia, dizziness, nausea, anorexia, and headache), with similar incidences and frequencies under both conditions for most events, although headache was reported 3 times more and nausea was reported 2 times more under the 4x10 mg dose. Dizziness was reported 5 times more and somnolence was reported 2 times more under the 1x40 mg dose. Finally, significant increases ($p<0.01$) in mean systolic blood pressure were observed at the 2-, 4- and 12-hour time points for both dosing conditions. For diastolic blood pressure, a significant increase ($p<0.01$) was noted for the 4 x 10 mg group at 4 hours post dose.

In conclusion, a single 1x40 mg dose of SLI381 capsules was bioequivalent to a single 4x10 mg dose of SLI381 capsules in pediatric subjects. Both doses were similarly tolerated.

3. TABLE OF CONTENTS

3.1 List of In-Text Tables

4. GLOSSARY AND DEFINITION OF TERMS

ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
ANOVA	Analysis of Variance
AUC	Area Under the Curve
B.I.D.	Twice a day
BP	Blood pressure / Systemic arterial pressure(s)
CFR	Code of Federal Regulations
CI	Confidence Interval
CNS	Central Nervous System
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	Case Report Form
CRO	Contract Research Organization
DR	Delayed Release
ECG	Electrocardiogram
EDTA	Ethylene Diamine Tetra-acetic Acid
FDA	U.S. Food and Drug Administration
GLM	General Linear Model
Hg	Mercury
HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICF	Informed Consent Form
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
LS Mean	Least Square Mean
mg	Milligram
mL	Milliliter
mm	Millimeter
ng	Nanogram
PI	Principal Investigator
PK	Pharmacokinetic
RBC	Red Blood Cell
SD	Standard Deviation
sec	Second
SOP	Standard Operating Procedure
WBC	White Blood Cell

5. ETHICS

5.1 Institutional Review Board (IRB)

The study protocol, informed consent form (ICF), and any amendments to the protocol were approved by IRBs, prior to study initiation, in conformance with 21 CFR 50 and 21 CFR 56. The approval letters are on file with the investigator and with the Sponsor. Information about the IRB is given in Section 16, Appendix IIC.

5.2 Ethical Conduct of the Study

This protocol was performed under the principles of the 18th World Medical Assembly (Helsinki 1964) and amendments of the 29th (Tokyo 1975), the 35th (Venice 1983) and the 41st (Hong Kong 1989) World Medical Assemblies and 48th General Assembly, Republic of South Africa, October 1996. A copy of this Declaration is in the investigator file.

5.3 Subject Information and Consent

All prospective subjects received written information and an explanation of what the study involved. Written informed consent was required from the parent/guardian and written assent was required from the subjects before study initiation. A copy of the Informed Consent Form was given to the subject. Signed and witnessed ICFs are on file with the investigator.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study was conducted at by Samuel W. Boellner, MD. Outpatients were seen at the Clinical Study Centers, LLC, located at 9601 Lile Drive, Suite 900 in Little Rock, AR. Subjects were confined at the Baptist Medical Plaza located at 1120 Medical Center Drive in Little Rock, AR. Names of investigator and study administrative structure are listed below:

Name and Affiliation	Title	Role
Samuel W. Boellner, MD Clinical Study Centers LLC, Medical Towers Bldg. I 9601 Lile Drive, Suite 900 Little Rock, AR 72205	Principal Investigator	Responsible for study conduct
M. Alex Michaels, MD Shire Pharmaceutical Development, Inc.	Vice President of Medical Affairs	Overall responsibility for clinical and safety aspects
Kathleen Wolf Shire Pharmaceutical Development, Inc.	Clinical Program Manager	Management of the study
Tom Green Shire Pharmaceutical Development, Inc.	Senior Data Analyst	Management of Database

7. INTRODUCTION

Shire Laboratories Inc. has developed a two-component extended-release formulation (SLI381 capsules or Adderall XR™) of ADDERALL® designed to produce pulsed-release of amphetamine salts yielding a therapeutic effect that lasts throughout the day with one morning dose for treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy [1].

ADDERALL® is a single entity amphetamine drug product mixture of neutral salts of dextroamphetamine sulfate, amphetamine sulfate, the dextro isomer of amphetamine saccharate, and d,l-amphetamine asparate. For each ADDERALL® tablet, the combination of salts and isomers results in a 3:1 ratio of dextro- to laevo-amphetamine.

The SLI381 capsule formulation is composed of two types of pellets of mixed salts of amphetamine being combined with a 50:50 ratio within one capsule. One type of the pellets is immediate-release pellets designed to release drug content in a similar mechanism to Adderall®. The second type of pellets is delayed-release pellets designed to release drug content 4-6 hours after the oral administration. With the inclusion of the delayed-release component, the two-unit formulation given once-a-day is expected to act similarly to the current marketed product of Adderall® given twice-a-day, 4-6 hours apart.

The purpose of this Phase I study was to evaluate the bioavailability of a single 1x40 mg SLI381 oral dose in comparison to a single 4x10 mg SLI381 oral dose in pediatric subjects.

The study was conducted in compliance with institutional review board and informed consent regulations.

8. STUDY OBJECTIVES

To determine the dose equivalence of one single dose (1x40 mg) of SLI381 40 mg capsules to one single dose (4x10 mg) of SLI381 10 mg capsules administered orally to children.

9. INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This trial was an open-label, randomized, single-dose, two-treatment, two-period crossover study in pediatric subjects comparing the bioequivalence of SLI381 given orally as a 1x40 mg dose to SLI381 given orally as a 4x10 mg dose.

The study used a balanced two-way crossover design with block size equal to 2. Twenty pediatric subjects (male and female), who were diagnosed as ADHD otherwise healthy and on similar dose levels as were given in this study, were randomized at study enrollment to one of the two treatment sequence groups. In each study period, these subjects were given a single oral 40 mg dose of SLI381, consisting of one 40-mg capsule (test condition) or four 10-mg capsules (reference condition) after an overnight fast (8 hours) according to their assigned treatment sequence. Each study period was separated by a 7-day washout period. Medication was administered at approximately 8:00 AM on the dosing days with 4 ounces of water.

TABLE 1 SCHEDULE OF EVENTS FOR PERIODS I AND II

Study Day:	-14 to -2	-1 and 7	1 and 8	2 and 9	3 and 10	10 - 11
Informed Consent	X					
Medical History	X	X[c]				
Physical Exam	X					X
Check in		X				
Discharge				X		
Clinical Laboratory Tests	X[ab]	X[d]				X[a]
SLI381 Assay			X[e]	X[g]	X[i]	
ECG	X					X
Height	X					X
Weight	X	X	X		X	X
Vital Signs (BP and P)	X	X	X[f]	X[h]	X[j]	X
Adverse Event Collection[k]	X	X	X	X	X	X
Study Medication			X			

[a] Will include standard chemistry, hematology, electrolytes, and urinalysis.
[b] Will include urine screening for drugs.
[c] Brief medical history.
[d] Urine pregnancy test for females who have experienced menarche.
[e] Blood draws for PK analysis at 0, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 12.0 hours post dose.
[f] Vital signs prior to blood draw at 0, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 12.0 hours post dose.
[g] Blood draw for PK analysis at 24 hours post dose.
[h] Vital signs prior to blood draw at 24 hours post dose.
[i] Blood draw for PK analysis at 48 hours post dose.
[j] Vital signs prior to blood draw at 48 hours post dose.
[k] SAEs will be collected for 30 days after discontinuation of study drug.
Source: Section 16, Appendix IIA, Protocol

Subjects were confined to the clinic 12 hours prior to each dosing day. Confinement continued for 24 hours post dose. Fourteen (14) blood samples (7 mL per sample) were collected through the 48-hour post-dose interval during each study period. These blood samples were used in determining the plasma levels of d-amphetamine and l-amphetamine at the following hours: 0-hour (approximately 5 minutes before dosing), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24 and 48 hours. Dosing for each study period was separated by a 7-day washout period. The assessment schedule for each study period is displayed in

Table 1. In this table Day –1 marks the beginning of the first confinement period, and Day –7 marks the beginning of the second confinement period.

9.1.1 Screening

Subjects were screened within 2 to 14 days before enrollment into the study. All prospective subjects received written information and an explanation of what the study involved. Written informed consent was required from the parent(s)/guardian(s) and written assent was required from the subjects before study initiation.

Screening measurements included:

- Orientation session and informed consent/assent
- Subject height and weight
- Medical history and physical examination
  - Vital signs (supine and standing blood pressure, supine and standing pulse, respiratory rate)
- Blood hematology
  - RBC count
  - Hemoglobin
  - Hematocrit
  - WBC count
  - Platelet count
- Serum chemistry
  - BUN
  - Creatinine
  - Glucose
  - AST
  - ALT
  - GGTP
  - Total bilirubin
  - Alkaline phosphatase
- Urinalysis
  - Microscopic examination
  - pH
  - Specific gravity
  - Protein
  - Glucose
  - Ketones
  - Bilirubin
  - Occult Blood
- Urine drug screen

- Urine pregnancy test on females of childbearing potential
- ECG
- Adderall® and dextroamphetamine were to be discontinued at least 7 days prior to Day 1. Methylphenidate was to be discontinued at least 3 days prior to Day 1.

After the screening, the investigator reviewed medical histories, clinical laboratory evaluations, and performed physical examinations. Subjects who met inclusion/exclusion criteria were enrolled into the study.

9.1.2 Treatment Periods

Treatment days were separated by a seven-day washout interval.
During the treatment period adverse events were assessed via observation and unsolicited reporting.

Day –1 and Day 7
Subjects eligible for study participation were admitted to the clinic in the evening, approximately 12 hours before the scheduled dose. At each treatment period check-in, vital signs, weight, and a brief medical history were obtained from each subject. A urine pregnancy test was also conducted, if applicable. Subjects remained at the clinic until completion of the 24-hour post-dosing blood collection and returned to the clinic for the 48-hour post-dose specimen collection.

After check-in, each subject received a standardized meal between the hours of 6:00 pm and 8:00 pm.

Treatment Days 1 and 8
After obtaining vital signs (blood pressure and pulse) and body weight of each subject, a Jelco™ catheter was inserted for collection of blood specimens. (EMLA Cream was applied to the IV site at least 60 minutes prior to catheter insertion.)

Subjects were required to fast for at least 8 hours before dosing and remain fasting for 4 hours after dosing. Subjects were allowed to consume water or dextrose 5% in water *ad lib* during the fasting period.

The study drug (1x40 mg dose of SLI381 extended-release capsules or 4x10 mg dose of SLI381 extended-release capsule) was administered to each subject at approximately 8:00 am with 4 ounces of water. Subjects were instructed to swallow the capsules intact, and their mouths were inspected after administration to ensure ingestion.

Blood was collected via catheter for SLI381 assay at pre-dose (hour zero), and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, and 48 hours post dose. Plasma samples were prepared by

centrifugation of whole blood samples (approximately 2500 rpm x 15 minutes at 4°C). All plasma samples were frozen and stored at -20°C until assayed at MDS Harris in Lincoln, Nebraska.

Post dose, vital signs (blood pressure and pulse) were collected prior to each blood draw.

A standardized lunch and standardized dinner was served 4 and 10 hours, respectively, post dose to each subject.

Day 2 and Day 9
After obtaining vital signs (blood pressure and pulse) and the 24-hour post-dose blood sample, the Jelco IV catheter was removed. Subjects were discharged from the confinement facility after the 24-hour post-dose blood draw.

Day 3 and Day 10
All subjects returned to the outpatient center for body weight measurement, vital signs (blood pressure and pulse), and blood collection for the 48-hour post dose specimen.

Closing, Days 10-11
At study closing, subjects' weight, height, and vital signs (blood pressure and pulse) were measured. Additionally, blood was collected for clinical laboratory tests (hematology, chemistry, urinalysis, and urine pregnancy test, if applicable) and an ECG and comprehensive physical were performed.

9.2 Choice of Control Groups

The study did not employ a control group per se. Instead, each subject acted as his/her own control, with the comparisons being made among the pharmacokinetics of the two doses.

9.3 Selection of Study Population

The protocol called for 20 pediatric subjects to be enrolled in the study. Subjects participating in this trial were selected based on the following inclusion and exclusion criteria.

9.3.1 Inclusion Criteria

Subjects of any race were required to meet the following criteria to be eligible to participate in the study:

INCLUSION CRITERIA
1. Good health, as determined by medical history, physical examination, and clinical laboratory measurements.
2. Age: 6 – 12 years. Females who had experienced menarche must have had a negative urine pregnancy test at screening and be practicing an acceptable method of contraception during the study.
3. Gender: males and females.
4. Previous stimulant exposure: Must have had prior exposure to stimulants (Adderall®, methylphenidate, dextroamphetamine) at similar dose levels as will be given in this study with no clinically significant tolerability difficulties. There was to be a one-week washout for Adderall® and dextroamphetamine and/or a 3-day washout for methylphenidate prior to the first dosing day.
5. Body weight and height: Weight and height were to be between the 5th and 95th percentile on the National Center for Health Statistics (NCHS) grown chart for age[2].
6. Drugs: Absence of any significant urine concentration of any drug that could interfere with the study.

Source: Section 16, Appendix IIA, Protocol

9.3.2 Exclusion Criteria

Subjects could not participate in the study if any of the following conditions existed:

EXCLUSION CRITERIA
1. History or clinical evidence of significant respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematologic, neurologic (including ataxia and/or seizures), or other chronic disease.
2. Use of any medication not considered acceptable by the clinical investigators during the 14-day period before the first dosing with the study drug (Day 1).
3. History of significant adverse reaction to Adderall® or any stimulant medication.
4. Participation in a study of investigational or marketed drugs during the 30-day period before the start of the study (Day 1).

Source: Section 16, Appendix IIA, Protocol

9.3.3 Restrictions

Patients were restricted from the following:

RESTRICTIONS
1. Administration of any medication without the approval of the Principal Investigator from Screening through Closing.
2. Adderall and dextroamphetamine were to be discontinued at least one week prior to Day 1.
3. Methylphenidate was to be discontinued at least three days prior to Day 1.
4. Fruit juice or foods containing ascorbic acid were prohibited within 3 days of dosing.
5. Beverages or foods containing caffeine were prohibited for at least 2 hours prior to each BP measurement and throughout both confinement periods.
6. Subjects were restricted from participating in any organized activities during the blood collection period.
6. Subjects were prohibited from an increase above usual activity level during the 48 hours prior to each clinical laboratory sampling.

Source: Section 16, Appendix IIA, Protocol

9.3.4 Removal of Subjects from Therapy or Assessment

Subjects and their parent(s)/guardian(s) were told that they were free to withdraw from the study at any time. The investigator, after consulting with Shire Laboratories, could terminate the study for a subject immediately if the subject experienced a serious adverse

event, a significant organ dysfunction, changes in any clinical or laboratory parameter, or other finding that suggested an unacceptable risk to the health of the subject. The investigator could also terminate the participation of a subject for noncompliance on the part of the parent, guardian, or subject.

For withdrawn subjects all data scheduled to be collected at study closing was to be collected at the time of early study termination, or on or before the scheduled study closing. Withdrawn subjects were not to be replaced.

9.4 Treatments

9.4.1 Treatments Administered

In the morning (approximately 8:00am) of Day 1, the subjects received one of the two treatments (1x40 mg SLI381 capsules or 4x10 mg SLI381 capsule) according to the randomization schedule. In the morning (approximately 8:00am) of Day 8, subjects received the alternate treatment.

Each treatment was administered with 4 ounces of water after an 8 hour fast.

9.4.2 Identity of Study Drug

Shire Laboratories Inc. supplied study drugs in 100-capsule bulk supply bottles.

Study Drug	**Lot #**
SLI381 40 mg capsules (test condition)	0F2722A
SLI381 10 mg capsules (reference condition)	0B2774A

The study drug identification was recorded in CRF and presented in Section 16, Appendix VII Table 1.1.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects were assigned to each treatment according to randomization schedules prepared for the study by Shire Pharmaceutical Development Inc. (Section 16, Appendix V). The randomization list was generated using a 2-by-2 Latin-square and an SAS random number generator (RANUNI), which had a seed number of 10005. The block size was two.

Dosing for each study period was separated by a seven-day washout period. Both the randomized treatment sequence and received treatment sequence for each subject are presented in Section 14, Table 1.1.1, and in Section 16, Appendix VII Table 2.1.

9.4.4 Dose Selection

The study selected the highest strength (40 mg capsules) of SLI381 products intended for marketing to evaluate the dose equivalence for meeting the regulatory requirement. The 10 mg capsules were the lowest strength of the SLI381 products when the study was being conducted.

9.4.5 Blinding

This was an open-label, crossover trial and the primary endpoints were objective measurements of bioavailability. Therefore, blinding of subjects, investigator, or sponsor was not required. The bottles were clearly labeled as containing 10 mg or 40 mg capsules of SLI381.

The treatments administered at each dosing day were recorded in CRF and presented in Section 16, Appendix VII Table 9.1.

9.4.6 Prior and Concomitant Therapy

The protocol stated that, administration of any medication without the approval of the Principal Investigator was prohibited from study screening through study closing. Adderall and dextroamphetamine were to be discontinued at least one week prior to Day 1. Methylphenidate was to be discontinued at least three days prior to Day 1. Concomitant medications taken before and during the study were recorded in CRF and are listed in Section 16, Appendix VII Table 3.1.

9.4.7 Treatment Compliance

Study center personnel administered each dose of study medication. Time of dose administration was recorded in CRF.

To ensure that each dose was taken, study personnel performed a mouth check after drug administration.

9.4.8 Drug Accountability

Study drug was shipped to the Principal Investigator by Shire Pharmaceutical Development, Inc. The Investigator was responsible for maintenance of study drug inventory and dispensing records. At the conclusion of the trial, all unused supplies and empty containers were to be returned to Shire Pharmaceutical Development, Inc. Clinical study center was to retain and store one sample of the 10 mg and 40 mg formulations in accordance with FDA regulations. Drug inventory and return are listed in the table below.

DRUG INVENTORY AND RETURN			
Compound/Dose/Lot Number	**Quantity**	**Quantity Spent**	**Quantity Left**
SLI381/40mg/0F2722A	500 capsules	20 capsules	480 capsules
SLI381/10mg/0B2774A	500 capsules	80 capsules	420 capsules

Source: Study documentation binder

9.5 Efficacy and Safety Variables

9.5.1 Pharmacokinetic Parameters

Blood samples were collected for later determination (by a validated LC/MS/MS method at MDS Harris) of plasma d-amphetamine and l-amphetamine concentrations pre-dosing and at the following hours after dosing: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, and 48. From the plasma drug levels, the following parameters for both d-amphetamine and l-amphetamine were measured and calculated at MDS Harris for bioavailability and bioequivalence evaluations for each formulation. Complete details of the assay method and calculation method are provided in Section 16, Appendix VIB, Detailed Pharmaceutical Analytical Report/Technical Report.

Variable	Description
AUC_{0-t}	Area under the drug concentration-time curve from time zero to t hour (t = last measurable concentration time point, Ct), calculated by the trapezoidal rule.
AUC_{0-inf}	Area under the drug concentration-time curve from time zero to infinity; using AUC_{0-t} + Ct /Kel (Kel = terminal elimination rate constant)
$t_{1/2}$	Elimination half-life; using LN(2)/Kel
C_{max}	Maximum observed drug concentration
T_{max}	Time to the maximum drug concentration (obtained without interpolation)

9.5.2 Safety Evaluations

The following safety parameters, the primary safety data, were collected throughout the study and were summarized by treatment group.

- Blood pressure (initial supine measurement at each time point, mmHg) and pulse (initial supine measurement at each time point, beats/min)
- Adverse events

Blood pressure readings were collected at screening, at check-in, prior to each blood collection in the two dosing periods, and at study closing. At each of these time points, three sets of blood pressure readings were collected after a 2-minute rest period:

1. Initial supine reading
2. 2 minute supine reading
3. Standing reading

Pulse readings were collected at screening, at check-in, prior to each blood collection in the two dosing periods, and at study closing. At each of these time points, three sets of pulse readings were collected after a 2-minute rest period:

1. Supine pulse
2. Standing pulse after 1 minute
3. Standing pulse after 2 minutes.

Respiratory rate was recorded with vital signs during screening period and at pre-dose. It served as a reference in the event that symptoms dictated repeat measurements.

All recorded blood pressure, pulse and respiration rate readings are listed in Section 16, Appendix VII, Table 6.1. The initial supine readings for blood pressure and pulse were used in summaries of vital signs, which appear in Section 14, Tables 5.1.1, 5.1.2, and 5.1.3.

Adverse event data were obtained by observation and close monitoring of subjects throughout the study. All adverse events, regardless or severity or relationship to study medication were to be recorded on the appropriate case report form. Adverse event reports were to include the description of event, date of onset, date event ended, severity, evaluation of drug relationship, and ultimate outcome.

Patients withdrawn from the study due to any adverse event were to be observed until the event resolved or an adequate explanation was obtained. For serious adverse events, the subjects were to be followed until clinical recovery was complete (including a return to baseline laboratory values) or until a clear outcome had been determined.

The Investigator was to review each event and assess its relationship to drug treatment according to the following definitions:

Related	An adverse event has a strong temporal relationship to study drug and recurs on rechallenge, and another etiology is unlikely or significantly less likely.
Possible	An adverse event has a strong temporal relationship to study drug, and an alternative etiology is equally or less likely compared to the potential relationship to study drug.
Not Related	An adverse event is due to underlying or concurrent illness or effect of another drug and is not related to study drug (e.g., has no temporal relationship to study drug or has a much more likely etiology).

Each reported adverse event was also graded on a 3-point severity scale by the investigator (mild, moderate, or severe). The severity grading, date and time of onset, time relationship to drug dosing, duration, and outcome of each event were recorded. The following definitions for rating severity were used:

Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's normal activities.
Severe	The adverse event causes considerable interference with the subject's normal activities, and may be incapacitating and/or life-threatening

Serious adverse events (as defined by the FDA Code of Federal Regulations (CFR), Chapter 21), whether or not they were deemed to be drug-related, were to be immediately reported by telephone to the Sponsor, followed by a written report.

Other safety data were also collected at either screening period and/or throughout the study. Listings were prepared for any abnormalities observed for these measures, which included the following:

- History
- Physical examination
- Vital signs (sitting respiratory rate, heart rate, blood pressure, temperature)
- 12-lead electrocardiogram
- Urinalysis (macroscopic: bilirubin, blood, glucose, ketones, pH, protein, specific gravity; microscopic if protein and/or blood are detected)
- Hematology (hemoglobin, hematocrit, WBC, RBC, platelet count, white cell differential)

- Serum chemistry (BUN, creatinine, glucose, AST, ALT, GGTP, bilirubin, and alkaline phosphatase)
- Serum pregnancy (for females at screening and close out)
- Urine screen for drugs (at screening only)

9.5.3 Appropriateness of Measurements

All effectiveness and safety assessments are widely used and generally recognized as reliable, accurate, and relevant. Alternative measures of bioavailability were not considered.

9.6 Data Quality Assurance

This study was sponsored by Shire Laboratories Inc. and conducted at Clinical Study Centers, LLC according to the ICH Guideline for Good Clinical Practice.

Quality Control Procedures, as described in Shire Laboratories Inc., Standard Operating Procedures were applied at each stage of data-handling to ensure that all data were processed correctly and are reliable. All data were collected using pre-printed CRFs. Complete CRFs were reviewed by study personnel and by the Sponsor's study monitor prior to data entry. Data were entered into database via a study-specific computerized data entry screen. Study database was validated prior to data entry. All data were double entered and compared for accuracy. Standard data validation procedures were used in data processing, such as valid data range check. All queries were resolved and posted to the database prior to database lock.

A complete blank CRF is attached in Section 16, Appendix IIB.

9.7 Statistical Methods and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

Amarex Clinical Research, a CRO located in Germantown, Maryland, prepared a statistical analysis plan (Section 16, Appendix VIA) for the Sponsor, based on protocol-specified analyses.

9.7.1.1 Analyses of Amphetamine Pharmacokinetics

Comparative Analysis of Pharmacokinetic Parameters

Pharmacokinetic (PK) parameters for d-amphetamine and l-amphetamine were first reported using the original metrics. Descriptive statistics (N, mean, median, standard deviation [SD], coefficient of variation [%CV]) of l-amphetamine and d-amphetamine were obtained for all PK parameters by treatment group.

Standard analysis of variance (ANOVA) model of a 2-way crossover design with a general linear approach (normal theory) was applied to each of the pharmacokinetic parameters of AUC, C_{max}, and T_{max} to examine, in general, the differences between the two treatment groups. The model included the following factors: sequence, subject-within-sequence, period, and treatment. The sequence effect was tested using the subject-within sequence effect. All other effects were tested using the residual error of the model.

A null hypothesis of zero difference for a parameter under study among the two treatment groups was assessed at the 0.05 level, with the alternative hypothesis of non-zero differences.

Bioequivalence Analysis of Pharmacokinetic Parameters

The extent and rate of drug absorption, as indexed by PK parameters of AUC and C_{max}, were analyzed on log scale, using the same model outlined above to assess the bioequivalence of the two treatment conditions. For each PK parameter examined for bioequivalence, the exact outcome obtained from the ANOVA model was tabulated and so were the descriptive statistics. The recommended two one-sided t-test hypotheses for average bioequivalence [3] were tested at the 0.05 level by constructing the 90% confidence interval (CI) of the ratio of the test-to-reference means.

9.7.1.2 Analyses of Safety Data

Adverse Events

All adverse events observed in this study, coded by preferred term (COSTART), were listed for individual subjects and tabulated by preferred term with respect to relationship to study medication and the severity of the adverse event. The frequencies of adverse events and their percentages were reported for the two treatment groups.

Early Termination

Reasons for discontinuation were to be summarized and tabulated by treatment group.

Blood Pressure and Pulse

Descriptive statistics summarized the vital signs data for each treatment group and each time-partitioned analysis period using raw data and change from pre-dose (baseline) data for each treatment period. Changes in the initial supine readings, from baseline to standard time points post-dose (2-, 4, 12, and 24-hours), were also analyzed comparatively within each treatment group using paired t-test.

No adjustments were made for multiple testing, and those p-values that were <0.01 were reported in this report.

9.7.1.3 Other Analyses

Demographic and Baseline Characteristics

Descriptive statistics were presented for the following demographic and baseline characteristics by treatment group:

- Age
- Race
- Sex
- Height
- Weight

All Other Measures

Abnormalities observed at the screening visit were listed for the following measures:

- History
- Physical examination
- Vital signs (sitting respiratory rate, heart rate, blood pressure, temperature)
- 12-lead electrocardiogram
- Urinalysis (macroscopic: bilirubin, blood, glucose, ketones, leukocyte esterase, nitrate pH, protein, specific gravity, urobilinogen; microscopic if protein, leukocytes, nitrate and/or blood are detected: RBC, WBC, cast, bacterial semi-quantitative measurements)
- Hematology (hemoglobin, hematocrit, WBC, RBC, platelet count)
- Serum chemistry (ALT, glucose, creatinine, albumin, thyroxin)
- Urine screen for alcohol and additional drugs (ethanol, amphetamines, opiates, cocaine)

9.7.2 Determination of Sample Size

Findings from previous Adderall® and SLI381 delayed-release pellets formulation studies indicated that the estimate of AUC test-to-reference ratio was within the range of 0.90-1.10 for d-amphetamine and l-amphetamine, and the estimated within-subject-between-formulation σ (log scale) was less than 0.10 for d-amphetamine and less than 0.13 for l-amphetamine. Given that the true AUC mean for a test condition is within the 90% region of the reference, for a sample size of 18 subjects, the proposed crossover design will have at least 80% power to reject the null-hypothesis of bioinequivalence at the 0.05 level.

Based upon the assumptions, the study planned to enroll 20 subjects, without replacement (10 subjects in each treatment sequence group).

9.8 Changes in the Conduct of the Study or the Planned Analyses

One amendment was made to the study protocol. Protocol Amendment I and the revised Informed Consent were IRB-approved on February 28, 2001. The amendment was intended to clarify the dose strength (i.e., a single dose of 1 x 40 mg vs. 4 x 10mg) used in the study and the time of study activities, and to correct typing errors and make administrative changes. All protocol-specified analyses were conducted.

During the conduct of this study, the investigator followed a set of specific criteria for reporting hypertension and tachycardia as adverse events, which included: for hypertension the blood pressure was ≥ 130 mmHg for systolic and/or ≥ 85 mmHg for diastolic and it increased by greater than 20% from baseline, and for tachycardia the pulse rate was ≥ 120 bpm and it increased by greater than 20% from baseline. This set of criteria for reporting hypertension and tachycardia as adverse events was not specified by the protocol.

In addition, the systolic blood pressure of 130-150 mmHg, 151-180 mmHg, and >180 mmHg was rated by the investigator as mild, moderate, and severe, respectively. The diastolic blood pressure of 85-90 mmHg, 91-95 mmHg, and >95 mmHg was rated by the investigator as mild, moderate, and severe, respectively. The pulse rate of 120-140 bpm, 141-170 bpm, and >170 bpm was rated by the investigator as mild, moderate, and severe, respectively.

10. SUBJECT GROUPS

10.1 Disposition of Subjects

Twenty (20) subjects were enrolled and randomized to treatment. All subjects completed the study.

One subject (012) could not be admitted for the second confinement period due to treatment with Augmentin for presumed streptococcal throat. Because of this apparent infective process, the principal investigator (with sponsor approval) postponed this subject's second dosing period for 14 days, which was completed satisfactorily. Subject 012 received his second dosing on March 26, 2001.

A listing of individual subject disposition is presented in Section 14, Table 1.1.2 and in Section 16, Appendix VII Table 2.1.

10.2 Protocol Deviations

The following protocol deviations occurred during the conduct of this study:

Height and Weight

- Subject 020 was above the 95% for weight
- Subject 010 was above the 95% for weight and height

The investigator interpreted these screening inclusion / exclusion criteria deviations to not be clinically significant and recommended that these subjects be included in the trial. Shire Pharmaceuticals Development Inc approved these deviations.

Screening Laboratory Measurements

Many subjects had lab values (hematology, chemistry, and urine) that were slightly higher or slightly lower than the normal lab value ranges. The investigator interpreted these values to be not clinically significant and he recommended that subjects be admitted into the study or continue. Shire Pharmaceutical Development Inc approved these deviations.

At the screening visit, the following subjects had positive amphetamine drug screens:

- Subject 002
- Subject 008
- Subject 009
- Subject 010
- Subject 011
- Subject 013
- Subject 015
- Subject 016
- Subject 020

The investigator determined that all patients did not have significant urine concentrations of any drug that could interfere with the study.

Blood Sample Times

Dosing Period 1

- Subject 016, +10 minutes (1 hour post dose)
- Subject 019, +10 minutes (1 hour post dose)
- Subject 010, +08 minutes (4 hour post dose)
- Subject 006, +05 minutes (5 hour post dose)
- Subject 009, +05 minutes (9 hour post dose)
- Subject 020, +05 minutes (24 hour post dose)
- Subject 005, +13 minutes (48 hour post dose)
- Subject 020, +27 minutes (48 hour post dose)
- Subject 004, +12 minutes (48 hour post dose)

Dosing Period 2

- Subject 002, +05 minutes (1 hour post dose)
- Subject 010, +05 minutes (6 hour post dose)
- Subject 010, +05 minutes (7 hour post dose)
- Subject 008, +05 minutes (48 hour post dose)
- Subject 020, +40 minutes (48 hour post dose)
- Subject 004, +15 minutes (48 hour post dose)

Concomitant Medications

Subject 002 was receiving Zithromax for an ear infection after the screening visit. This course of antibiotic therapy was completed 5 days before the first dosing period.

Subject 003 received Tylenol on the second dosing day. The drug relationship was considered not related and there was no change to the dosing.

Subject 008 was receiving Zoloft for mood and anger changes. This psychotropic therapy was completed 10 days before the first dosing period.

Subject 012 received Ibuprofen, Tylenol and Motrin for fever during the 7-day washout interval for fever. In addition, this subject received Augmentin for streptococcal throat during this same time period. This course of antibiotic therapy was completed 6 days before the second dosing period.

Subject 015 was receiving Zoloft for aggressive behavior at the time of the screening visit. This psychotropic therapy was completed 8 days before the first dosing period.

Subject 017 received Robatussin for cough after the screening visit. This course of a therapy was completed 3 days before the first dosing period.

Subject 020 was receiving Trisadome for insomnia at the time of screening visit. This course of therapy was completed 8 days before the first dosing period.

11. EFFICACY EVALUATION

11.1 Data Sets Analyzed

The Intent-to-Treat (ITT) population was analyzed for all PK and safety parameters. The ITT population was defined as the set of subjects who were randomized to treatment, received at least one dose of study medication, and the corresponding PK parameters were available. All treatment groups identified in Section 9.4.1 of this report were assessed.

It was noted that Subject 020 showed an unusually high pre-dose concentrations and unusual shape of PK profile at 24 hours post dose for both isomers under the treatment of

the 4x10 mg dose (Section 16, Appendix VII, Tables 4.1 and 4.2). However, data from this subject was included in the analysis of bioavailability. The summary results with these values being excluded are presented in Section 16, Appendix VIB.

11.2 Demographic and Other Baseline Characteristics

Table 2 summarizes participating subjects' demographics and other baseline characteristics.

Seventy percent (14/20) of subjects enrolled were male and 30% (6/20) were female. Race distribution was primarily Caucasian (95%, 19/20), with one Black subject (5%). The ages of study participants ranged between 7 and 12 years with a mean age of 10.2 years (s.d.=1.6). Subjects weighed between 51 and 181 pounds with the mean of 89.9 pounds, and their heights ranged from 48 to 65 inches with the mean of 57.1 inches. Since it was a crossover design, no inferential statistical analyses were conducted on demographic data.

A listing of individual subject demographic and baseline characteristics is presented in Section 14, Table 1.1.1.

TABLE 2 SUMMARY OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Characteristics	Category/Parameters	(Total N=20)	
Race (%)	Caucasian	19	(95)
	Black	1	(5)
Gender (%)	Male	14	(70)
	Female	6	(30)
Height (inches)	Mean	57.1	
	SD	4.6	
	Median	57.5	
	Min-Max	48.0 – 65.0	
Weight (pounds)	Mean	89.9	
	SD	35.1	
	Median	81.5	
	Min-Max	51.0 – 181.0	
Age (years)	Mean	10.2	
	SD	1.6	
	Median	10.0	
	Min-Max	7.0 – 12.0	

Source: Section 14 Table 1.1.1

11.3 Measurements of Treatment Compliance

Site study personnel measured treatment compliance by conducting a mouth check after each administration of study medication to assure subjects swallowed the study medication, by recording the formulation the subject took for a treatment period in the CRF, and by capsule counts for each study phase and at the end of the study.

Both the assigned treatment sequence and received treatment sequence for a subject are presented in Section 14, Table 1.1.1. All subjects received the assigned the treatments.

11.4 Pharmacokinetic (PK) Results

Mean plasma levels (ng/mL) of amphetamine following drug administration are shown in Section 14, Table 2.1.1 for d-isomer and Table 2.2.1 for l-isomer. Data listings of d-amphetamine concentrations and the PK parameters for individual subjects are contained in Section 16, Appendix VII Table 4.1, and the data for l-amphetamine are contained in Section 16, Appendix VII Table 4.2.

Graphical representations of formulation mean plasma levels of amphetamine following drug administration are shown in Section 14, Figure 1.1 for all treatments, Figure 1.2 for d-amphetamine, and Figure 1.3 for l-amphetamine. Graphical presentations of individual subject d- and l-amphetamine concentrations are found in Section 14, Figures 2.1 and 2.2, and Figures 3.1 and 3.2, respectively.

11.4.1 D-amphetamine

Table 3 contains descriptive statistics of each dose condition for the d-amphetamine PK parameters of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, T_{max}, and $t_{1/2}$. The descriptive statistics of each individual subject for d-amphetamine PK parameters of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, T_{max}, and $t_{1/2}$ are provided in Section 14, Tables 2.1.2 through 2.1.6.

TABLE 3 MEAN AND S.D. OF PK PARAMETERS FOR D-AMPHETAMINE

PK parameters	Measures	SLI381 1x40 mg (Test)	SLI381 4x10 mg (Reference)
AUC 0-inf (ng hr/mL)	Mean	1573.95	1688.25
	S.D.	377.52	466.72
$AUC_{0\text{-}t}$ (ng hr/mL)	Mean	1608.98	1662.87
	S.D.	395.60	451.34
C_{max} (ng/mL)	Mean	98.61	92.94
	S.D.	28.21	23.34
T_{max} (hr)	Mean	5.35	5.64
	S.D.	3.25	2.85
$t_{½}$ (hr)	Mean	8.23	8.80
	S.D.	1.07	2.33

*p<0.05 compared to 4 x 10 mg SLI381

Source: Section 14, Tables 2.1.2 through 2.1.7

The arithmetic mean ± standard deviation of $AUC_{0\text{-}inf}$ (ng•hr/mL) for the reference dose (4x10 mg) is 1688.25 ± 466.72. For the test dose (1x40 mg), arithmetic mean ± standard deviation of $AUC_{0\text{-}inf}$ (ng•hr/mL) is 1573.95 ± 377.52.

The arithmetic mean ± standard deviation of $AUC_{0\text{-}t}$ (ng•hr/mL) for the reference (4x10 mg) is 1662.87 ± 451.34. For the test dose (1x40 mg), arithmetic mean ± standard deviation of $AUC_{0\text{-}t}$ (ng•hr/mL) is 1608.98 ± 395.60.

The arithmetic mean ± standard deviation of C_{max} (ng/mL) for the reference (4x10 mg) is 92.94 ± 23.34. For the test dose (1x40 mg), arithmetic mean ± standard deviation of C_{max} (ng/mL) is 98.61 ± 28.21.

The arithmetic mean ± standard deviation of T_{max} (hr) for the reference (4x10 mg) is 5.64 ± 2.85. For the test dose (1x40 mg), arithmetic mean ± standard deviation of T_{max} (hr) is 5.35 ± 3.25.

The ANOVA results of the 2-way crossover design for d-amphetamine PK parameters are presented in Section 14, Table 2.1.7. These results indicate there were no statistical differences among the two treatment groups for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, or T_{max}.

The bioequivalence results on the logarithmic transformations of the d-amphetamine PK data are reported in Table 4 and in Section 14, Tables 2.1.9.

TABLE 4 BIOEQUIVALENCE OF PK PARAMETERS FOR D-AMPHETAMINE

PK parameters	Measures	1x40 mg vs. 4x10 mg
$AUC_{0\text{-}inf}$ (ng hr/mL)	Ratio estimate	1.00
	90% CI of the ratio estimate	0.96 – 1.03*
$AUC_{0\text{-}t}$ (ng hr/mL)	Ratio estimate	0.97
	90% CI of ratio estimate	0.93 – 1.02*
C_{max} (ng/mL)	Ratio estimate	1.06
	90% CI of ratio estimate	0.96 – 1.16*

* denotes 90% confidence interval fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on logarithmic scale

Source: Section 14, Table 2.1.9

These results demonstrate that the 90% confidence intervals of the test (1x40 mg) to reference (4x10 mg) ratio fell within the recommended 0.80-1.25 limits of average bioequivalence for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max}.

Thus, the study demonstrates that a single 1x40 mg dose of SLI381 capsules was bioequivalent to a single 4x10 mg dose of SLI381 capsules for d-amphetamine.

11.4.2 L-amphetamine

Table 5 contains descriptive statistics of each formulation for the l-amphetamine PK parameters of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, T_{max}, and $t_{1/2}$. The descriptive statistics of each individual subject for l-amphetamine PK parameters of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, T_{max}, and $t_{1/2}$ are provided in Section 14, Tables 2.2.2 through 2.2.6.

The arithmetic mean ± standard deviation of $AUC_{0\text{-}inf}$ (ng•hr/mL) for the reference dose (4x10 mg) is 512.01 ± 123.71. For the test dose (1x40 mg), arithmetic mean ± standard deviation of $AUC_{0\text{-}inf}$ (ng•hr/mL) is 538.91 ± 148.34.

TABLE 5 MEAN AND S.D. OF PK PARAMETERS FOR L-AMPHETAMINE

PK parameters	Measures	SLI381 1x40 mg (Test)	SLI381 4x10 mg (Reference)
AUC 0-inf (ng hr/mL)	Mean	538.91*	512.01
	S.D.	148.34	123.71
$AUC_{0\text{-}t}$ (ng hr/mL)	Mean	539.33	529.31
	S.D.	155.37	175.90
C_{max} (ng/mL)	Mean	30.27*	27.16
	S.D.	8.57	6.94
T_{max} (hr)	Mean	5.45	5.80
	S.D.	3.21	2.84
$t_{½}$ (hr)	Mean	9.40	9.29
	S.D.	1.51	1.31

* $p<0.05$ compared to 4 x 10 mg SLI381

Source: Section 14, Tables 2.2.2 through 2.2.7

The arithmetic mean ± standard deviation of $AUC_{0\text{-}t}$ (ng•hr/mL) for the reference (4x10 mg) is 529.31 ± 175.90. For the test dose (1x40 mg), arithmetic mean ± standard deviation of $AUC_{0\text{-}t}$ (ng•hr/mL) is 539.33 ± 155.37.

The arithmetic mean ± standard deviation of C_{max} (ng/mL) for the reference (4x10 mg) is 27.16 ± 6.94. For the test dose (1x40 mg), arithmetic mean ±standard deviation of C_{max} (ng/mL) is 30.27 ± 8.57.

The arithmetic mean ± standard deviation of T_{max} (hr) for the reference (4x10 mg) is 5.80 ± 2.84. For the test dose (1x40 mg), arithmetic mean ± standard deviation of T_{max} (hr) is 5.45 ± 3.21.

The ANOVA results of the 2-way crossover design for l-amphetamine PK parameters are presented in Section 14, Table 2.2.7. These results indicate there were statistical differences ($p<0.05$) among the two treatment groups for $AUC_{0\text{-}inf}$ and C_{max} but not for $AUC_{0\text{-}t}$ and T_{max}.

The bioequivalence results on the logarithmic transformations of the l-amphetamine PK data are reported in Table 6 and in Section 14, Tables 2.2.9. These results demonstrate that the 90% confidence intervals of the test (1x40 mg) to reference (4x10 mg) ratio fell within the recommended 0.80-1.25 limits of average bioequivalence for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max}.

TABLE 6 BIOEQUIVALENCE OF PK PARAMETERS FOR L-AMPHETAMINE

PK parameters	Measures	1x40 mg vs. 4x10 mg
$AUC_{0\text{-}inf}$ (ng hr/mL)	Ratio estimate	1.06
	90% CI of the ratio estimate	1.02 – 1.10*
$AUC_{0\text{-}t}$ (ng hr/mL)	Ratio estimate	1.03
	90% CI of ratio estimate	0.96 – 1.10*
C_{max} (ng/mL)	Ratio estimate	1.11
	90% CI of ratio estimate	1.03 – 1.21*

* denotes 90% confidence interval fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on logarithmic scale

Source: Section 14, Table 2.2.9

Thus, the study demonstrates that a single 1x40 mg dose of SLI381 capsules was bioequivalent to a single 4x10 mg dose of SLI381 capsules for l-amphetamine.

11.4.3 Conclusions of PK Data

The study shows that the 1x40 mg dose of SLI381 capsules, given as a single dose, demonstrated comparable bioavailability to the 4x10 mg dose of SLI381 capsules. The average plasma levels of the 1x40 mg dose were bioequivalent in both d- and l-amphetamine as determined by AUC and C_{max} PK parameters to the 4x10 mg dose, based upon the current criteria for the 90% CI of the test-to-reference ratio. For d-amphetamine, there were no statistical differences among the two treatment groups for any of the PK parameters. For l-amphetamine, there were statistical differences among the two treatment groups for $AUC_{0\text{-}inf}$ and C_{max} but not for $AUC_{0\text{-}t}$ and T_{max}.

12. SAFETY EVALUATION

12.1 Extent of Exposure

All twenty subjects received two single 40 mg doses of SLI381 separated by at least a 7-day washout period.

12.2 Adverse Events

Section 14 contains detailed listings and summarization of the adverse events reported during this study. A guide to these tables is provided in the listing below.

Table #	Title
3.1.1	Adverse Events Recorded in CRF by Individual Subjects
3.1.2	Adverse Events Recorded in CRF by Study Phase
3.1.3	Treatment Emergent Adverse Events by Costart Label, Severity and Relationship to Treatment
3.1.4	Treatment Emergent Adverse Events by Costart Label and Individual Subjects
3.2.1	Number (%) of Subjects Reporting Adverse Events by Costart Label: All Treatments
3.2.2	Number (%) of Subjects Reporting Adverse Events by Costart Label: 1x40 mg SLI381
3.2.3	Number (%) of Subjects Reporting Adverse Events by Costart Label: 4x10 mg SLI381
3.3.1	Adverse Events Observed During Treatment Period
3.3.2	Adverse Events Observed Prior to Treatment Period
3.4.1	Treatment-Emergent Adverse Events Observed On Dosing Days
3.5.1	Treatment-Emergent Adverse Events Observed Off Dosing Days

12.2.1 Brief Summary of Adverse Events

All twenty subjects reported one or more adverse events during the study. A total of 167 events were reported, with 5 of them recorded pre dose of the first treatment period.

Treatment emergent AEs with frequency rate of 2+% over total episodes are listed below:

Preferred Term (Costart)	Count	(%) (n=162)
Hypertension	55	(34.0)
Tachycardia	41	(25.3)
Insomnia	15	(9.3)
Headache	6	(3.7)
Dizziness	6	(3.7)
Nausea	6	(3.7)
Anorexia	5	(3.1)

Source: Section 14, Table 3.1.3

Seventeen of the 162 reported treatment-emergent adverse events (10.5%) were unrelated to the study medication. The Investigator rated the other 145 events as possibly related (9/162, 5.6%) or related (136/162, 84%) to study medication.

Most treatment emergent events were mild or moderate in severity (154/162, 95.1%) and the majority of events (142/162, 87.7 %) occurred on dosing day. All treatment-emergent

adverse events resolved. One event reported by Subject #003 observed prior to the first dosing period (1x40 mg SLI381) remained unresolved at the time of study closing. The unresolved event was rhinitis.

12.2.2 Number and Percent of Subjects Reporting Adverse Events

Of the 162 treatment-emergent adverse events, 20/20 (100%) subjects under the 1x40 mg dose reported 82 (50.6%) events and 20/20 (100%) subjects under the 4x10 mg dose reported 80 (49.4%) events. The adverse events with the highest incidence rate of subjects reporting under the 1x40 mg and 4x10 mg doses were hypertension (55% and 50%, respectively), tachycardia (55% and 45%, respectively), insomnia (35% and 30%, respectively), dizziness (25% and 5%, respectively), nausea (10% and 20%, respectively), anorexia (10% and 15%, respectively), and headache (5% and 15%, respectively).

Number and percent of subjects reporting adverse events is presented for each preferred term in Table 7.

TABLE 7 NUMBER AND % OF SUBJECTS REPORTING ADVERSE EVENTS*

	(Test Dose) 1 x 40 mg SLI381			(Reference Dose) 4 x 10 mg SLI381			All Doses		
Preferred Term (Costart)	No. of Subjects (n=20)	(%) of Subjects Reporting	No. of AEs Reported (n=82)	No. of Subjects (n=20)	(%) of Subjects Reporting	No. of AEs Reported (n=80)	No. of Subjects (n=20)	(%) of Subjects Reporting	No. of AEs Reported (n=162)
Anorexia	2	(10.0)	2	3	(15.0)	3	4	(20.0)	5
Asthenia	1	(5.0)	1				1	(5.0)	1
Constip				1	(5.0)	1	1	(5.0)	1
Cough Inc	1	(5.0)	1				1	(5.0)	1
Cramps Legs	1	(5.0)	1				1	(5.0)	1
Diarrhea	1	(5.0)	1	1	(5.0)	1	2	(10.0)	2
Dizziness	5	(25.0)	5	1	(5.0)	1	5	(25.0)	6
Dyspepsia	1	(5.0)	1	1	(5.0)	1	2	(10.0)	2
Emotion Labil	1	(5.0)	1				1	(5.0)	1
Fever				1	(5.0)	1	1	(5.0)	1
Headache	1	(5.0)	1	3	(15.0)	5	4	(20.0)	6
Hypertens	11	(55.0)	24	10	(50.0)	31	16	(80.0)	55
Hypesthesia	1	(5.0)	1	1	(5.0)	1	1	(5.0)	2
Infect				1	(5.0)	1	1	(5.0)	1
Insomnia	7	(35.0)	9	6	(30.0)	6	12	(60.0)	15
Migraine	1	(5.0)	1				1	(5.0)	1
Nausea	2	(10.0)	2	4	(20.0)	4	5	(25.0)	6
Nervousness				1	(5.0)	1	1	(5.0)	1
Pain Abdo				1	(5.0)	1	1	(5.0)	1
Pallor	1	(5.0)	1				1	(5.0)	1
Rhinitis	1	(5.0)	1				1	(5.0)	1
Somnolence	2	(10.0)	2	1	(5.0)	1	2	(10.0)	3
Syncope	1	(5.0)	1				1	(5.0)	1
Tachycardia	11	(55.0)	23	9	(45.0)	18	14	(70.0)	41
Tinnitus	1	(5.0)	1				1	(5.0)	1
Twitch	1	(5.0)	2	1	(5.0)	1	1	(5.0)	3
Vasodilat				1	(5.0)	1	1	(5.0)	1

Preferred Term (Costart)	(Test Dose) 1 x 40 mg SLI381			(Reference Dose) 4 x 10 mg SLI381			All Doses		
	No. of Subjects (n=20)	(%) of Subjects Reporting	No. of AEs Reported (n=82)	No. of Subjects (n=20)	(%) of Subjects Reporting	No. of AEs Reported (n=80)	No. of Subjects (n=20)	(%) of Subjects Reporting	No. of AEs Reported (n=162)
Vomit				1	(5.0)	1	1	(5.0)	1
Total**	20		82	20		80	20		162

*Treatment-emergent

**The total number of subjects reporting is not equal to the sum of the individual cells as one subject may have more than one adverse event.

Source: Section 14, Tables 3.2.1, 3.2.2, 3.2.3

It should be noted that the investigator followed a set of specific criteria for reporting hypertension and tachycardia as adverse events in the study, which included: for hypertension the blood pressure was ≥ 130 mmHg for systolic and/or ≥ 85 mmHg for diastolic and it increased by greater than 20% from baseline, and for tachycardia the pulse rate was ≥ 120 bpm and it increased by greater than 20% from baseline. This set of criteria for reporting hypertension and tachycardia as adverse events was not specified by the protocol.

In addition, the systolic blood pressure of 130-150 mmHg, 151-180 mmHg, and >180 mmHg was rated by the investigator as mild, moderate, and severe, respectively. The diastolic blood pressure of 85-90 mmHg, 91-95 mmHg, and >95 mmHg was rated by the investigator as mild, moderate, and severe, respectively. The pulse rate of 120-140 bpm, 141-170 bpm, and >170 bpm was rated by the investigator as mild, moderate, and severe, respectively.

As a result, the incidences of subjects reporting hypertension (80%) and tachycardia (70%) were the two highest among the adverse events observed in this study.

12.2.3 Analysis of Adverse Events

The number of treatment-emergent adverse events for the test dose (1 x 40 mg SLI381) was 82/162 (50.6%), which was similar to the number of events for the 4 x 10 mg SLI381 group (80/162, 49.4%). The incidence rate of subjects reporting adverse events under both dosing conditions was the same (20/20). The incidences and frequencies were similar under both conditions for most events, although headache was reported 3 times more and nausea was reported 2 times more under the 4x10 mg dose. Dizziness was reported 5 times more and somnolence was reported 2 times more under the 1x40 mg dose. No comparative analyses were performed.

12.3 Deaths, Other Serious Adverse Events and Other Significant Adverse Events

No deaths or other serious adverse events occurred during this study.

12.4 Clinical Laboratory Results

A listing of all laboratory results for individual subjects is found in Section 16, Appendix VII Table 5.1 (hematology), Table 5.2 (serum chemistry), Table 5.3 (urinalysis), Table 5.4 (urine drug screen), and Table 5.5 (pregnancy).

No clinically significant, treatment-emergent laboratory abnormalities were reported by the investigator at the screening period and at study close out.

12.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

12.5.1 Vital Signs

During each treatment period, supine and standing blood pressures and pulse were measured at pre-dose and before each blood collection. Descriptive and comparative statistics of mean vital signs and change from baseline (pre-dose) were prepared using the first supine blood pressure and pulse results for the baseline (pre-dose), and the 2-, 4,12-, and 24-hour post dose measurements. These data are displayed by treatment condition in Section 14, Tables 5.1.1 through 5.1.3 for systolic blood pressure, diastolic blood pressure, and pulse, respectively.

Compared to pre dose, significant increases ($p<0.01$) in mean systolic blood pressure were observed at the 2-, 4- and 12-hour time points for both dosing conditions. For diastolic blood pressure, a significant increase ($p<0.01$) was noted for the 4 x 10 mg group at 4 hours post dose. No significant changes from baseline were noted in pulse measurements for either group during the 24-hour post treatment period.

Systolic Blood Pressure

At the $p=0.01$ level, statistically significant increases in changes from pre dose to post dose were observed in systolic blood pressure under both dosing conditions at the 2-, 4-, and 12-hour post dose time points. The maximum of average increases in systolic blood pressure were seen at 2 hours post dose (+10.65 mmHg) under the 4x10 mg dose and at 2 hours post dose (+11.45 mmHg) under the 1x 40 mg dose. At 24 hours post dose, both dosing conditions had returned to near baseline levels. (Section 14, Table 5.1.1)

Diastolic Blood Pressure

At the $p=0.01$ level, no statistically significant changes from pre dose to the measured post dose time points were observed in diastolic blood pressure for the 1 x 40 mg dosing condition (treatment). For the reference group (4 x 10 mg SLI381), a statistically significant increase from pre dose to post dose was observed in diastolic blood pressure at the 4-hour post dose time point with a maximum average increase of 8.50 mmHg. (Section 14, Table 5.1.2)

Pulse

At the p=0.01 level, no statistically significant changes from baseline were observed in either treatment group during the 24-hour post treatment time period (Section 14, Table 5.1.3).

12.5.2 Physical Examinations

Physical examinations were performed on all subjects at the screening period and at the study close-out visit. At the screening and close out visits, no clinically significant physical exam abnormalities were noted by the investigator. Results are displayed in Section 14, Table 6.1.1.

12.5.3 Medical History

Medical histories were collected from all subjects at the screening visit. On-going medical histories included seasonal allergies (2) and left swollen nipple (1).

A listing of medical history abnormalities appears in Section 14, Table 7.1.

12.5.4 Other Safety Measures

A 12-lead ECG was conducted on each subject at the screening and close-out visits. ECG data for individual subjects are displayed in Section 16, Appendix VII, Listing 7.1.

Ten subjects (50%) had abnormal EKG observations at the screening visit. Ten subjects (50%) had abnormal EKG findings at the end of study and all of these abnormal findings observed at the end of study were reviewed by a pediatric cardiologist and deemed not clinically significant.

12.6 Safety Conclusions

There were no deaths, no serious adverse events, and no withdrawals from this study.

All 20 subjects reported one or more adverse events during the study. The majority of treatment-emergent adverse events (145/162, 89.6%) were judged as related or possibly related to study medication. Most treatment-emergent adverse events were mild or moderate in severity (154/162, 95.1%). The number of adverse events was similar under the two dosing conditions.

Because of the investigator's use of specific criteria for reporting hypertension (systolic $\geq$ 130 mmHg and diastolic $\geq$ 85 mmHg and 20% increase from baseline) and tachycardia ($\geq$ 120 bpm and 20% increase from baseline) as adverse events, hypertension and tachycardia were seen as the most common adverse events reported in this study. The incidence of subjects reporting was 80% for hypertension and 70% for tachycardia. The other commonly reported adverse events included insomnia, dizziness, nausea, anorexia, and headache. All of these adverse events were not unexpected.

The incidence rate of subjects reporting adverse events was the same for both dosing conditions (100%, 20/20). The incidences and frequencies were similar under both conditions for most events, although headache was reported 3 times more and nausea was reported 2 times more under the 4x10 mg dose. Dizziness was reported 5 times more and somnolence was reported 2 times more under the 1x40 mg dose.

Compared to pre dose, significant increases ($p<0.01$) in mean systolic blood pressure were observed at the 2-, 4- and 12-hour time points for both dosing conditions. For diastolic blood pressure, a significant increase ($p<0.01$) was noted for the 4 x 10 mg group at 4 hours post dose. No significant changes from baseline were noted in pulse measurements for either group during the 24-hour post treatment period. Clinically significant changes in vital signs were recorded as adverse events.

No treatment emergent physical abnormalities or treatment-emergent abnormalities in laboratory results were reported as clinically significant by the investigator. Ten subjects (50%) had abnormal EKG findings at the end of study and all of these abnormal findings observed at the end of study were reviewed by a pediatric cardiologist and deemed not clinically significant.

13. DISCUSSION AND OVERALL CONCLUSIONS

Shire Pharmaceutical Development Inc. has developed a two-component extended-release formulation (SLI381 or Adderall XR™) of ADDERALL® designed to produce pulsed-release of amphetamine salts yielding a therapeutic effect that lasts throughout the day with one morning dose, for treatment of attention deficit hyperactivity disorder (ADHD).

The objective of this study was to evaluate the bioavailability of a single 1x40 mg SLI381 oral dose in comparison to a single 4x10 mg SLI381 oral dose in pediatric subjects.

Efficacy

This study demonstrated that a single 1x40 mg dose of SLI381 capsules was bioequivalent as measured by all relevant PK parameters to a single 4x10 mg dose of SLI381 capsules in pediatric subjects for both d- and l-amphetamine. For l-amphetamine, statistically significant differences were noted between the two doses for the $AUC_{0\text{-}inf}$ and C_{max} PK parameters but not for $AUC_{0\text{-}t}$ and $t_{1/2}$.

Safety

There were no deaths, no other serious adverse events, and no withdrawals from this study.

All 20 subjects reported one or more adverse events during the study. The incidence of subjects reporting adverse events was the same for both dosing conditions. The majority of adverse events were mild or moderate in severity and judged to be treatment related or possibly related. The most frequently reported adverse events were not unexpected (i.e.,

hypertension, tachycardia, insomnia, dizziness, nausea, anorexia, and headache). The frequency of adverse events was similar under both dosing conditions. Finally, significant increases ($p<0.01$) in mean systolic blood pressure were observed at the 2-, 4- and 12-hour time points for both dosing conditions. For diastolic blood pressure, a significant increase ($p<0.01$) was noted for the 4 x 10 mg group at 4 hours post dose. No significant changes were noted in pulse for either of the dosing conditions.

In conclusion, a single 1x40 mg dose of SLI381 capsules was bioequivalent to a single 4x10 mg dose of SLI381 capsules in pediatric subjects. Both doses were similarly tolerated.